

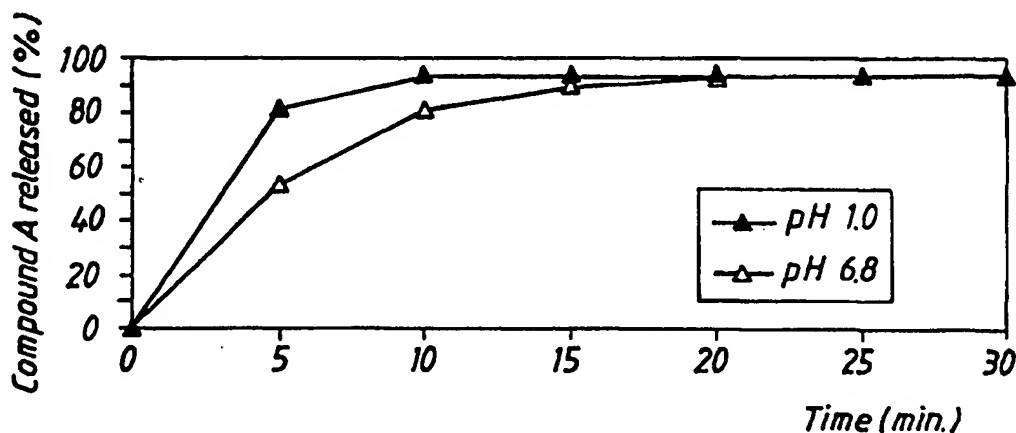


## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

|   |  |   |
|---|--|---|
| <p>(51) International Patent Classification <sup>7</sup> :<br/><b>A61K 9/20, 47/38, 38/55, A61P 7/02</b></p>  | <p><b>A1</b></p>   | <p>(11) International Publication Number: <b>WO 00/13671</b></p> <p>(43) International Publication Date: 16 March 2000 (16.03.00)</p> |
| <p>(21) International Application Number: PCT/SE99/01471</p> <p>(22) International Filing Date: 27 August 1999 (27.08.99)</p> <p>(30) Priority Data:<br/>9802973-9 3 September 1998 (03.09.98) SE</p> <p>(71) Applicant (for all designated States except US): ASTRA AKTIEBOLAG [SE/SE]; S-151 85 Södertälje (SE).</p> <p>(72) Inventors; and<br/>(75) Inventors/Applicants (for US only): FORSMAN, Sigbrit [SE/SE]; Astra Hässle AB, S-431 83 Mölndal (SE). KARLSSON, Christer [SE/SE]; Astra Hässle AB, S-431 83 Mölndal (SE). KARLSSON, Magnus [SE/SE]; Astra Hässle AB, S-431 83 Mölndal (SE).</p> <p>(74) Agent: ASTRA AKTIEBOLAG; Intellectual Property, Patents, S-151 85 Södertälje (SE).</p> | <p>(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).</p> <p><b>Published</b><br/>With international search report.<br/>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</p> |   |

(54) Title: IMMEDIATE RELEASE TABLET

Example 1



## (57) Abstract

A new oral IR formulation in solid form for a low molecular weight thrombin inhibitor having pH dependent dissolution, characterized in that the formulation comprises a filler or a combination of fillers having disintegrant properties in an amount higher than 35 % w/w of the formulation.

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## IMMEDIATE RELEASE TABLET

### Field of the invention

5 The invention relates to a solid dosage form of a low molecular weight thrombin inhibitor formulated as immediate release (IR) tablets as well as a process for manufacture thereof. The invention also relates to the medical use of the formulation in the prophylaxis and / or treatment of thromboembolism.

### Background of the invention

10 The thrombin inhibitor, used in the formulation of the present invention is a low molecular weight drug with pH dependent solubility. It is characterised by a low solubility at basic pH which is dramatically increased in the protonated form at acidic pH. Thus, upon administration in conventional IR formulations, fast dissolution of the drug is obtained in acidic pH while markedly slower dissolution is obtained at more neutral pH. This variability in dissolution is not acceptable for safe, efficient and convenient therapy. The present invention provides an immediate release formulation based on conventional manufacturing processes with careful chosen excipients that provides a dissolution which is not, or very little dependent on pH.

Several different ways have been suggested in order to prepare immediate-release solid dosage forms.

25 Lachman (The theory and practice of industrial pharmacy 1986, 343, appA) describes the composition and manufacturing of two different standard granulates for IR tablets. These two compositions gave very poor quality of the granulates, which gave unacceptable tablets with very low hardness. These compositions do not work with the low molecular weight thrombin inhibitors used in connection with the present invention. The tablets do

not answer to the definition of a rapidly dissolving drug product presented in Guidance for Industry. Waiver of in Vivo Bioavailability and Bioequivalens Studies for Immediate Release Solids Dosage Forms Containing Certain Active Moieties/Active Ingredients Based on Biopharmaceutics Classification System. Tablets must release 85% or more of  
5 stated amount within 30 min.

### Description of the invention

It has now been found that low molecular weight peptide-based thrombin inhibitors with  
10 pH-dependent solubility - including their salts - can be formulated as IR tablets with no or very little pH depending dissolution.

Therefore, the object of the present invention is to provide a novel pharmaceutical formulation comprising a low molecular weight peptide-based thrombin inhibitor  
15 formulated as an IR-tablet with no or very little pH depending dissolution and a process for the preparation of such formulation.

Thrombin inhibitors referred to in this application are low molecular weight peptide-based thrombin inhibitors with pH dependent solubility. The term "low molecular weight  
20 peptide-based thrombin inhibitors" will be well understood by one skilled in the art to include thrombin inhibitors with one to four peptide linkages, and/or with a molecular weight below 1000, and includes those described generically and, more preferably, specifically in the review paper by Claesson in Blood Coagul. Fibrin. (1994) 5, 411, as well as those disclosed in US Patent No. 4,346,078; International Patent Applications WO  
25 97/23499, WO 97/02284, WO97/46577, WO 98/01422, WO 93/05069, WO93/11152, WO 95/23609, WO95/35309, WO 96/25426, WO 94/29336, WO WO 93/18060 and WO 95/01168; and European Patent Applications 623 596, 648 780, 468 231, 559 046, 641 779, 185 390, 526 877, 542 525, 195 212, 362 002, 364 344, 530 167, 293 881, 686 642, 669 317 and 601 459.

Preferred low molecular weight peptide-based thrombin inhibitors include those known collectively as the "gatrans". Particular gatrans which may be mentioned include HOOC-CH<sub>2</sub>(R)Cha-Pic-Nag-H (known as inogatran; see International Patent Application WO 93/11152 and the list of abbreviations therein) and HOOC-CH<sub>2</sub>-(R)Cgl-Aze-Pab-H (known as melagatran; see International Patent Application WO 94/29336 and the list of abbreviations therein).

The preferred low molecular weight peptide-based thrombin inhibitor is selected from the group consisting of inogatran, (*Glycine, N-[2-[2-[[[3-[(aminoimino-methyl)amino]propyl]amino]carbonyl]-1-piperidinyl]-1-(cyclohexylmethyl)-2-oxoethyl]-, [2R-[2S]]-*), melagatran, (*Glycine, N-[2-[2-[[[4 (aminoiminomethyl)phenyl]-methyl]amino]carbonyl]-1-azetidiny]-1-cyclohexyl-2-oxoethyl]-, [2R-[2S]]-*) and compound A, (*Glycine, N-[1-cyclohexyl-2-[2-[[[4-[(hydroxyimino)aminomethyl]-phenyl]methyl]amino]carbonyl]-1-azetidiny]-2-oxoethyl]-, ethyl ester, [S-(R\*, S\*)]-*).

The particularly preferred low molecular weight thrombin inhibitor Compound A is effective for the treatment of thrombo-embolism. Compound A is described in the International Patent Application WO 97/23499. Compound A is a low molecular weight thrombin inhibitor with good oral bioavailability, low variability and limited food interaction. No solid dosage forms containing this thrombin inhibitor have been reported.

In order to produce tablets which provides a dissolution which is not or very little dependent on pH compound A should have a particle size less than 300 µm, preferably less than 150 µm and with a preferred mean particle size less than 80 µm. With other low molecular weight thrombin inhibitor with low solubility at basic pH and pH dependent solubility the requirements on the particle size will depend on the level of low solubility.

It has been found that by carefully selecting excipients the pH dependent dissolution could be reduced and giving a tablet release of more than 85% within 30 minutes in acidic as

well as neutral environment. This in spite of Compound A having an extremely pH dependent solubility.

The formulation according to the invention comprises the thrombin inhibitor, a filler or a  
5 combination of fillers, said filler/fillers having disintegrant properties (due to swelling)  
and, optionally, non swelling filler(s) disintegrant(s), binder(s) and/or lubricant(s).

The amount of filler/fillers having disintegrant properties constitutes more than 35% (w/w), preferably more than 50% (w/w) of the formulation.

10

Some excipients can serve multiple purposes, e.g. be a filler and a disintegrant at the same time. An excipient used in higher amounts than 35 % is in the invention defined as a filler but may contribute with other important properties for the formulation e.g. disintegration, binding or lubrication.

15

The filler with disintegrant properties is selected from the group consisting of cellulose per se (such as microcrystalline cellulose), microfine cellulose) starch per se (such as maize starch, sodium starch glycollate, potato starch, rice starch, wheat starch).

20 The nonswelling filler is selected from the group sugars (such as mannitol, sorbitol, dextrose, xylitol, sucrose, laktos).

The disintegrant is selected from the group consisting of cellulose per se (such as microcrystalline cellulose, microfine cellulose, cross-linked sodium carboxymethyl  
25 cellulose, cross-linked hydroxypropyl cellulose), starch per se (such as sodium starch glycollate, pregelatinised starch, maize starch, potato starch, rice starch, wheat starch) and others (such as cross linked polyvinylpyrrolidone, cationic exchange resin).

The binder is selected from the group consisting of cellulose per se (such as sodium  
30 carboxymethylcellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, methyl

cellulose), polymers (such as polyvinylpyrrolidone, polyethylene glycol), gelatins (such as hydrolysed gelatin), and traditional binders (such as starch, natural gums).

The lubricant is selected from the group consisting of insoluble lubricants (such as  
5 magnesium stearate, calcium stearate, zinc stearate, stearic acid, oils, talc, sodium stearyl fumarate), and soluble lubricants (such as polyethylene glycol, sodium benzoate, sodium lauryl sulphate).

In the formulation according to the invention the different constituents are preferably  
10 included in the following proportions, calculated by per cent w/w of the finished tablet:

Thrombin inhibitor: 1 - 35 %, preferably 1 - 15 %.

Filler: 35 - 90 %, preferably 45 - 80 %, when microcrystalline cellulose 50 - 90 %,  
15 preferably 60 - 80 % and most preferably 72 - 76 %, when nonswelling filler 0-50% when mannitol 0 - 15 %, preferably 5 - 10 %.

Disintegrant: 0 - 35 %, preferably 7 - 35 %, when sodium starch glycollate 3 - 20 %, preferably 5 - 10 %.

20 Binder: 0- 15 %, preferably 4 - 12 %, when polyvinylpyrrolidone 3 - 15 %, preferably 5 - 10 %.

Lubricant: 0 - 5 %, preferably 0.5 - 1.5 %, when sodium stearyl fumarate 0.5 - 1.5 %, 25 preferably above 1 %.

In the invention it was found that a formulation comprising the active component with a particle size less than 300  $\mu\text{m}$ , preferably less than 150  $\mu\text{m}$  and with a preferred mean particle size less than 80  $\mu\text{m}$ , fillers (e.g. microcrystalline cellulose (50-90%, preferably  
30 74%), mannitol (0 - 15 %, preferably 8.5 %) disintegrant

(e.g. sodium starch glycollate 3 - 20 %, preferably 8.5 %), moistened with with a suitable binder (e.g. polyvinylpyrrolidone K 90 ( 3- 15 %, preferably 8 %) and final mixed with suitable lubricant (e.g. sodium stearyl fumarate ( 0.5 - 1.5 %, preferably 1 %) provided a tablet having good technical properties and a very small pH dependent dissolution.

5

The formulations according to the invention can preferably be prepared either by direct compression or by wet granulation technique.

#### Direct compression

10

A low molecular weight thrombin inhibitor is mixed with the filler of fillers and if necessary the disintegrant. This mixture is then mixed with the lubricant and compressed to the tablets.

15

#### Wet granulation

20

A low molecular weight thrombin inhibitor is mixed with the filler of fillers, and if necessary the disintegrant. The mixture is then moistured with a suitable solvent in which the binder may be dissolved. After drying the granulate is milled and then mixed with the lubricant and compressed to tablets

Working ExamplesExample 1 Drug dissolution from tablets according to the invention

- 5 IR tablets of the thrombin inhibitor, Compound A, were prepared by mixing Compound A microcrystalline cellulose, sodium starch glycollate and mannitol. The mixture was moistured with a suitable amount of polyvinylpyrrolidone K 90 dissolved in water. After drying, the granulate was milled and then mixed with sodium stearyl fumarate and compressed to tablets.

10

|   | mg/tabl |
|---|---------|
| Compound A                              | 24      |
| Microcrystalline cellulose (MCC pH 101) | 140     |
| 15 Sodium starch glycollate             | 16      |
| Mannitol                                | 16      |
| Polyvinylpyrrolidone K 90               | 15      |
| Water                                   | q.s.    |
| Sodium stearyl fumarate                 | 2       |

20

|                |        |
|----------------|--------|
| Punches:       | 9mm    |
| Tablet weight: | 213 mg |
| Hardness:      | 110N   |

- 25 The obtained tablets were analysed with regard to dissolution of Compound A using a USP dissolution apparatus No. 2 (paddle), 100 rpm, 500 ml. The dissolution medium used had a temperature of 37°C. Two different dissolution medium were used, 0.1 M HCl pH 1 and phosphate buffer pH 6.8 (ionic strength 0.1). The amount of Compound A released was determined by UV-spectrometry.

30

Results are shown in Figure 1. After 30 minutes the amount of Compound A dissolved was 94 % (average n=3) in 0.1 M HCl and 94 % (average n=3) in phosphate buffer pH 6.8.

Example 1b Drug dissolution from tablets according to the invention

5

IR tablets of thrombin inhibitor, Compound A were prepared by mixing Compound A, microcrystalline cellulose and maize starch and the mixture was moistured with a suitable amount of maize starch (paste). After drying the granulate was milled and then mixed with polyvinylpyrrolidone crosslinked. Finally the sodium stearyl fumarate was admixed and  
10 the granulate was compressed into tablets.

|                                  | mg/tabl |
|----------------------------------|---------|
| Compound A                       | 30      |
| 15 Microcrystalline cellulose    | 115     |
| Maize starch                     | 55      |
| Maize starch (paste)             | 6       |
| Water                            | q.s.    |
| Polyvinylpyrrolidone crosslinked | 10      |
| 20 Sodium stearyl fumarate       | 2.2     |
| Punches:                         | 8.5 mm  |
| Tablet weight:                   | 219 mg  |
| Hardness:                        | 110 N   |

25

The obtained tablets were analysed for dissolution of Compound A according to the method described in Example 1. Results are shown in Figure 2. After 30 minutes the amount of Compound A dissolved was 100 % (average n=3) in 0.1 M HCl and 97 % (average n=3) in phosphate buffer pH 6.8.

30

**Example 2** Drug dissolution from tablets according to the reference

Lachman ((The theory and practice of industrial pharmacy 1986,343,appA) describes another composition and manufacturing of a "standard" granulate for an IR tablet. IR tablets  
5 of the thrombin inhibitor, Compound A were prepared according to this method by mixing Compound A, tricalcium phosphate and the mixture was moistured with pre-gelatinized maize starch dissolved in water. After drying the granulate was milled and then mixed with talc Finally, the mineral oil was admixed and the granulate was compressed to tablets.

|    |                       |        |
|----|-----------------------|--------|
| 10 | Compound A            | 24     |
|    | Tricalcium phosphate  | 100    |
|    | Pregelatinized starch | 15     |
|    | Water                 | q.s.   |
|    | Talc                  | 60     |
| 15 | Mineral oil, light    | 4      |
|    | Punches:              | 9 mm   |
|    | Tablet weight:        | 198 mg |
|    | Hardness:             | 12 N   |

20

The obtained tablets were analysed for dissolution of Compound A according to the method described in Example 1. Results are shown in Figure 2. After 30 minutes the amount of Compound A dissolved was 40 % (average n=3) in 0.1 M HCl and 5 % (average n=3) in phosphate buffer pH 6.8.

25

**Example 3** Drug dissolution from tablets according to the reference

Lachman (The theory and practice of industrial pharmacy 1986,343,appA) describes composition and manufacturing of a another "standard" granulate for an IR tablet. IR  
5 tablets of thrombin inhibitor, Compound A were prepared according to this method by mixing Compound A, lactose and the mixture was moistured with starch dissolved in water.

After drying the granulate was milled and then mixed with dry starch and talc. Finally the mineral oil was admixed and the granulate was compressed to tablets.

10

|                    |        |
|--------------------|--------|
| Compound A         | 24     |
| Lactose            | 110    |
| Starch(paste)      | 5      |
| 15 Starch          | 28     |
| Talc               | 28     |
| Mineral oil 50 cps | 11     |
| Punches:           | 9mm    |
| 20 Tablet weight   | 206 mg |
| Hardness:          | 13 N   |

The obtained tablets were analysed for dissolution of Compound A according to the method described in Example 1. Results are shown in Figure 3. After 30 minutes the  
25 amount of Compound A dissolved was 100 % (average n=3) in 0.1 M HCl and 74 % (average n=3) in phosphate buffer pH 6.8.

*Short description of the Figures*

Figure 1: Dissolution of the thrombin inhibitor Compound A from tablets according to the invention as described in Example 1. (No figure is given for example 1b).

5

Figure 2: Dissolution of the thrombin inhibitor Compound A from tablets according to the reference as described in Example 2

10

Figure 3: Dissolution of the thrombin inhibitor Compound A from tablets according to the reference as described in Example 3

Conclusion (Examples)

From the Examples it is obvious that a sufficient quality of the product is not achieved  
15 when using a "standard" granulate. Either the technical properties are bad [Example 2 and  
3,] and/or the dissolution in phosphate buffer pH 6.8 does not meet the definition of a  
rapidly dissolving drug product in Guidance for Industry. Waiver of in Vivo  
Bioavailability and Bioequivalens Studies for Immediate Release Solids Dosage Forms  
Containing Certain Active Moieties/Active Ingredients Based on Biopharmaceutics  
20 Classification System. With the formulation according to the invention the dissolution is  
fast in both medias and the technical properties are excellent.

CLAIMS

1. An oral immediate release formulation in solid form of a low molecular weight peptide-based thrombin inhibitor having pH dependent solubility c h a r a c t e r i z e d in that the  
5 formulation comprises a filler or a combination of fillers having disintegrant properties in an amount higher than 35% w/w of the formulation, selected from the group consisting of a cellulose per se and a starch per se.
2. An oral formulation according to claim 1, c h a r a c t e r i z e d in that the formulation  
10 optionally contains a sugar, a disintegrant, a binder and/or a lubricant.
3. An oral formulation according to any of the preceding claims, c h a r a c t e r i z e d in that the thrombin inhibitor is having a particle size of less than 300  $\mu\text{m}$ , preferably less than 150  $\mu\text{m}$  and a preferred mean particle size less than 80  $\mu\text{m}$ .  
15
4. An oral formulation according to claims any of the preceding claims  
c h a r a c t e r i z e d in that it comprises a combination of microcrystalline cellulose and mannitol.
- 20 5. An oral formulation according to claim 4, c h a r a c t e r i z e d in that microcrystalline cellulose constitutes 50 - 90 % (w/w) of the formulation.
6. An oral formulation according to claim 4, c h a r a c t e r i z e d in that mannitol constitutes 0 - 15 % (w/w) of the formulation.  
25
7. An oral formulation according to any of the preceding claims wherein the thrombin inhibitor is glycine, N-[1-cyclohexyl-2-[2-[[[4-[(hydroxyimino)aminomethyl]-phenyl]methyl]amino]carbonyl]-1-azetidiny]-2-oxoethyl]-, ethyl ester, [S-(R\*, S\*)]-).
- 30 8. An oral formulation according to any of the preceding claims for use in therapy.

9. The use of a low molecular weight peptide-based thrombin inhibitor, a filler or a combination of fillers having disintegrant properties in an amount higher than 35% w/w according to claim 1 in the manufacture of a formulation for prophylaxis and / or treatment  
5 of thrombo-embolism.

10. A method for prophylaxis and / or treatment of thrombo-embolism wherein a therapeutically effective amount of a formulation according to claim 1 is administered to a mammal in the need of such treatment.

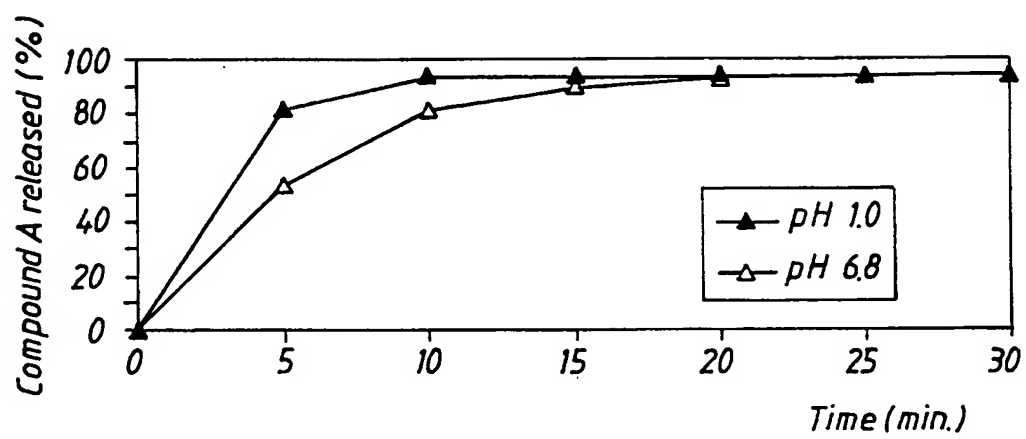
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11. A process for the preparation of an oral immediate release formulation according to claim 1 characterized in that the preparation is by direct compression or by wet granulation technique.

15 12. Use of a filler selected from the group consisting of a cellulose derivative, and a starch derivative, optionally a sugar, a disintegrant, a binder and/or a lubricant in the preparation of an oral immediate release formulation containing a low molecular weight peptide-based thrombin inhibitor having pH dependent solubility.

20

1 / 2

*Fig. 1**Example 1*

2 / 2

Fig. 2

Example 2

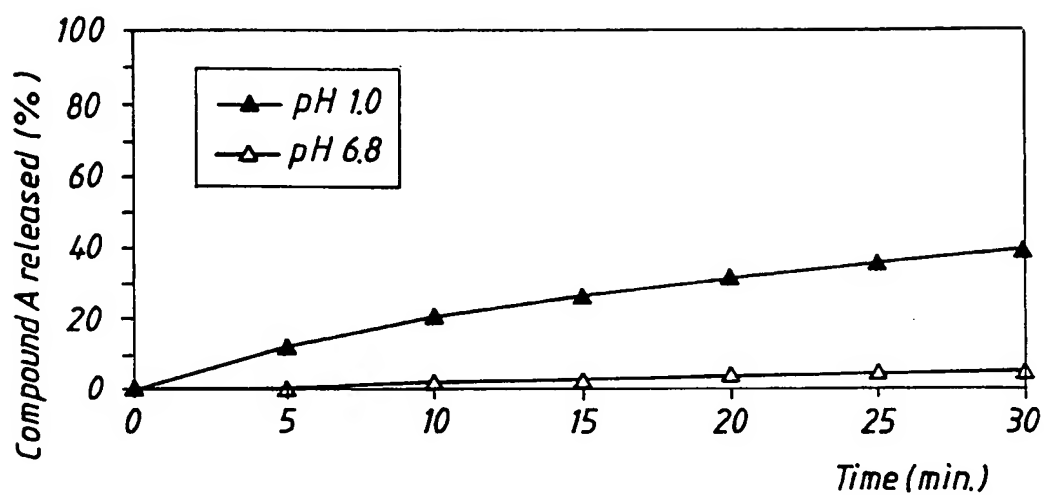
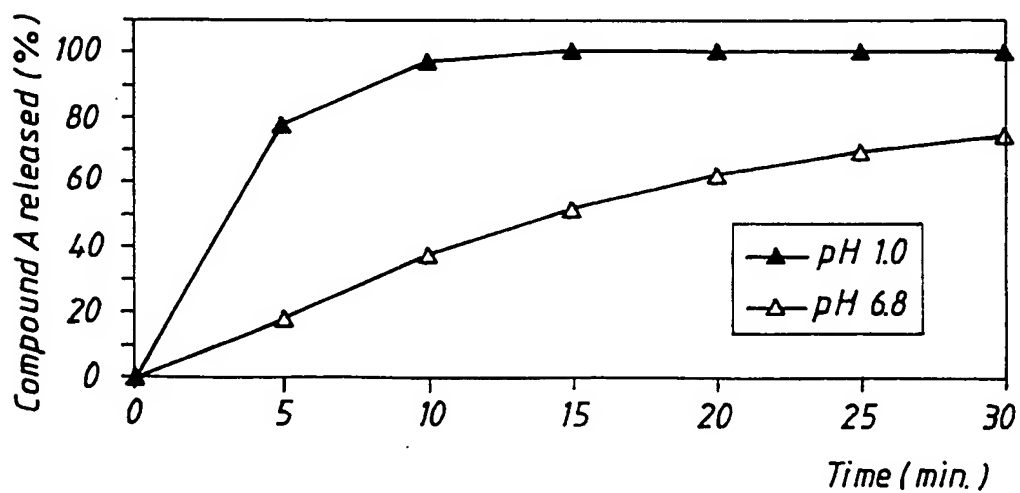


Fig. 3

Example 3



## INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 99/01471

## A. CLASSIFICATION OF SUBJECT MATTER

IPC7: A61K 9/20, A61K 47/38, A61K 38/55, A61P 7/02  
According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages  | Relevant to claim No. |
|-----------|---|-----------------------|
| X         | EP 0803251 A1 (JANSSEN PHARMACEUTICA N.V.),<br>29 October 1997 (29.10.97), see page 5, line 18 -<br>page 7, line 37<br>-- | 1-12                  |
| A         | WO 9813029 A1 (DUPHAR INTERNATIONAL RESEARCH B.V.),<br>2 April 1998 (02.04.98), see abstract and example<br>20<br>--      | 1-12                  |
| A         | WO 9723499 A1 (ASTRA AKTIEBOLAG), 3 July 1997<br>(03.07.97), see claim 39<br>--<br>-----                                  | 1-12                  |

☐ Further documents are listed in the continuation of Box C.☒ See patent family annex.

- \* Special categories of cited documents:
- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed
- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- "&" document member of the same patent family

|  |  |
|--|--|
| Date of the actual completion of the international search  | Date of mailing of the international search report                       |
| 9 December 1999  | 20 -01- 2000   |
| Name and mailing address of the ISA/<br>Swedish Patent Office<br>Box 5055, S-102 42 STOCKHOLM<br>Facsimile No. +46 8 666 02 86 | Authorized officer<br>Hampus Rystedt/Eö<br>Telephone No. +46 8 782 25 00 |

## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/SE 99/01471**Box I** Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 10  
because they relate to subject matter not required to be searched by this Authority, namely:  
**Although claim 10 relates to a method for treatment of the human or animal body (see PCT Rule 39.1(iv)), a search has been carried out. The search has been based on the effects of the claimed composition.**
2. ☐ Claims Nos.:  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

**Box II** Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Remark on Protest**

- ☐ The additional search fees were accompanied by the applicant's protest.  
☐ No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

02/11/99

International application No.

PCT/SE 99/01471

| Patent document<br>cited in search report | Publication<br>date | Patent family<br>member(s) | Publication<br>date |
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